Applicants:

Arlindo L. Castelhano et al.

Serial No.:

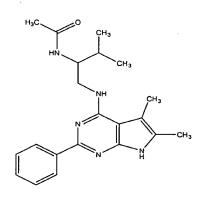
09/728,616

Filed Page 5 December 1, 2000

76. (New) A compound having the structure:

wherein R_1 is 3-hydroxy cyclopentyl ethylamino carbonylamino propyl, N, N-diethylamino carbonylamino ethyl, thioacetamido 3-amino ethyl, acetyloxy cyclopentyl, 3-hydroxy cyclopentyl, 2-pyrrolyl carbonyl aminoethyl, imidazolidinone ethyl, 1-aminocarbonyl-2-methyl propyl, 1aminocarbonyl-2-phenyl ethyl, 3-hydroxy azetidino, imidazolyl ethyl, acetamido 1-(R)-phenyl-2ethyl, hydroxyethyl, or N-methylaminocarbonyl pyridyl-2- methyl;

wherein R_5 and R_6 are independently H, substituted or unsubstituted alkyl, or aryl.





Serial No.: 09/728,616

Filed: December 1, 2000

Page 6

78. (New) The compound of claim 76, having the structure:

79. (New) The compound of claim 76, having the structure:

Conta

Serial No.: 09/728,616

Filed: December 1, 2000

Page 7

80. (New) The compound of claim 76, having the structure:

Serial No.: 09/728,616

Filed: December 1, 2000

Page 8

82. (New) The compound of claim 76, having the structure:



Serial No.: 09/728,616

Filed: December 1, 2000

Page 9

84. (New) The compound of claim 82, having the structure:



Serial No.: 09/728,616

Filed: December 1, 2000

Page 10

86. (New) The compound of claim 82, having the structure:



Serial No.: 09/728,616

Filed: December 1, 2000

Page 11

88. (New) The compound of claim 76, having the structure:

Serial No.: 09/728,616

Filed: December 1, 2000

Page 12

90. (New) The compound of claim 76, having the structure:

Serial No.: 09/728,616

Filed: December 1, 2000

Page 13

92. (New) The compound of claim 76, having the structure:



Serial No.: 09/728,616

Filed: December 1, 2000

Page 14

94. (New) The compound of claim 76, having the structure:

Serial No.: 09/728,616

Filed: December 1, 2000

Page 15

96. (New) The compound of claim 76, having the structure:

97. (New) The compound of claim 96, having the structure:

Serial No.: 09/728,616

Filed: December 1, 2000

Page 16

99. (New) A compound having the structure:

- 100. (New) A method for treating a disease associated with an A3 adenosine receptor in a subject in need of such treatment, comprising administering to the subject a therapeutically effective amount of the compound of claim 76 or 99 so as to thereby treat the disease associated with the A3 adenosine receptor in the subject, wherein the disease associated with the A3 adenosine receptor is cardiac hypoxia, cerebral ischemia, diuresis, myocardial ischemia, bronchoconstriction or diabetes.
- 101. (New) The method of claim 100, wherein the subject is a mammal.
- 102. (New) The method of claim 101, wherein the mammal is a human.
- 103. (New) A prodrug of the compound of claim 76 or 99, wherein the prodrug is metabolized *in vivo* by a human subject to an active drug which selectively inhibits the A3 adenosine

Applicants:

Arlindo L. Castelhano et al.

Serial No.:

09/728,616

Filed:

Page 17

December 1, 2000

receptor wherein the prodrug is

an ester of an alcohol or carboxylic acid group, if such a group is present in the compound;

an acetal or ketal of an alcohol group, if such a group is present in the compound;

an N-Mannich base or an imine of an amine group, if such a group is present in the compound; or

a Schiff base, oxime, acetal, enol ester, oxazolidine, or thiazolidine of a carbonyl group, if such a group is present in the compound.

- 104. (New) The prodrug of claim 103, wherein the prodrug is water-soluble.
- 105. (New) The prodrug of claim 103, wherein said prodrug is metabolized *in vivo* by esterase catalyzed hydrolysis.
- 106. (New) A pharmaceutical composition comprising the prodrug of claim 103 and a pharmaceutically acceptable carrier.
- 107. (New) The pharmaceutical composition of claim 106, wherein said pharmaceutical composition is an ophthalmic formulation.
- 108. (New) The pharmaceutical composition of claim 106, wherein said pharmaceutical composition is an periocular, retrobulbar or intraocular injection formulation.
- 109. (New) The pharmaceutical composition of claim 106, wherein said pharmaceutical composition is a systemic formulation.
- 110. (New) A method for inhibiting the activity of an A3 adenosine receptor in a cell that is subjected to abnormal stimulation of the A3 adenosine receptor, which comprises contacting the cell with a compound of claim 76 or 99, so as to inhibit the activity of the A3 adenosine receptor.

D'il



Serial No.: 09/728,616

Filed: December 1, 2000

Page 18

111. (New) A method for treating a gastrointestinal disorder associated with an A3 adenosine receptor in a subject in need of such treatment, comprising administering to the subject a therapeutically effective amount of the compound of claim 76 or 99, so as to thereby treat the gastrointestinal disorder in the subject.

- 112. (New) The method of claim 111, wherein said disorder is diarrhea.
- 113. (New) The method of claim 112, wherein the subject is a human.
- 114. (New) A method for treating a respiratory disorder associated with an A3 adenosine receptor in a subject in need of such treatment, comprising administering to the subject a therapeutically effective amount of the compound of claim 76 or 99, so as to thereby treat the respiratory disorder in the subject, wherein the respiratory disorder is asthma, chronic obstructive pulmonary disease, allergic rhinitis or an upper respiratory disorder.
- 115. (New) The method of claim 114, wherein the subject is a human.
- 116. (New) A method for treating inflammation of the eye associated with an A3 adenosine receptor in a subject in need of such treatment, which comprises administering to the subject a therapeutically effective amount of the compound of claim 76 or 99 so as to thereby treat the inflammation of the eye in the subject.
- 117. (New) A method for treating a disease associated with an A3 adenosine receptor in a subject in need of such treatment, comprising administering to the subject a therapeutically

Serial No.: 09/728,616

Filed: December 1, 2000

Page 19

effective amount of a compound of claim 76 or 99 so as to thereby treat the disease associated with the A3 adenosine receptor in the subject, wherein the disease associated with the A3 adenosine receptor is associated with mast cell degranulation or eosinophil activity.

- 118. (New) The method of claim 117 wherein the subject is human.
- 119. (New) A method for treating a disease associated with an A3 adenosine receptor in a subject in need of such treatment, comprising administering to the subject a therapeutically effective amount of a compound of claim 76 or 99 so as to thereby treat the disease associated with the A3 adenosine receptor in the subject, wherein the disease associated with the A3 adenosine receptor is asthma, glaucoma, retinopathy, ocular ischemia, or macular degeneration.
- 120. (New) The method of claim 119, wherein the subject is human.
- 121. (New) The method of claim 119, wherein the disease is asthma.
- 122. (New) The method of claim 119, wherein the disease is glaucoma.
- 123. (New) A combination therapy for glaucoma, comprising the compound of claim 76 or 99, and a prostaglandin agonist, $\beta 2$ agonist, or a muniscrinic antagonist.
- 124. (New) A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 76 or 99 and a pharmaceutically acceptable carrier.
- 125. (New) The pharmaceutical composition of claim 124, wherein said therapeutically effective amount is effective to treat

Conti

Applicants:

Arlindo L. Castelhano et al.

Serial No.:

09/728,616

Filed

December 1, 2000

Page 20

a respiratory disorder or a gastrointestinal disorder.

- 126. (New) The pharmaceutical composition of claim 125, wherein said gastrointestinal disorder is diarrhea.
- 127. (New) The pharmaceutical composition of claim 125, wherein said respiratory disorder is asthma, allergic rhinitis, or chronic obstructive pulmonary disease.
- 128. (New) The pharmaceutical composition of claim 124, wherein said pharmaceutical composition is an ophthalmic formulation.
- 129. (New) The pharmaceutical composition of claim 124, wherein said pharmaceutical composition is an periocular, retrobulbar or intraocular injection formulation.
- 130. (New) The pharmaceutical composition of claim 124, wherein said pharmaceutical composition is a systemic formulation.
- 131. (New) The pharmaceutical composition of claim 124, wherein said pharmaceutical composition is a surgical irrigating solution.
- 132. (New) A packaged pharmaceutical composition for treating a disease associated with A3 adenosine receptor in a subject, comprising:
 - (a) a container holding a therapeutically effective amount of the compound of claim 76 or 99; and
 - (b) instructions for using said compound for treating said disease in a subject.
- 133. (New) A method of preparing the compound of claim 76, comprising the steps of

Conto

Serial No.: 09/728,616

Filed: December 1, 2000

Page 21

a) reacting R_6 H_2N R_5 and NC R_6 to provide NC R_6

wherein P is a removable protecting group;

b) treating the product of step a) under cyclization conditions to provide

c) treating the product of step b) under suitable conditions to provide

$$\bigcap_{N} \bigcap_{H} R_{5} \quad ; \text{ and }$$

d) treating the chlorinated product of step c) with NH2R1 to provide



Serial No.: 09/728,616

Filed: December 1, 2000

Page 22

wherein R₁ is 3-hydroxy cyclopentyl ethylamino carbonylamino propyl, N, N-diethylamino carbonylamino ethyl, thioacetamido ethyl, 3-amino acetyloxy cyclopentyl, 3-hydroxy cyclopentyl, 2-pyrrolyl carbonyl aminoethyl, imidazolidinone ethyl, 1-aminocarbonyl-2-methyl propyl, aminocarbonyl-2-phenyl ethyl, 3-hydroxy azetidino, imidazolyl ethyl, acetamido ethyl, 1-(R)-phenyl-2hydroxyethyl, or N-methylaminocarbonyl pyridyl-2- methyl;

wherein R_5 and R_6 are independently H, substituted or unsubstituted alkyl, or aryl.

Pold